



Clinical trial results:

A Prospective Randomized Placebo Controlled Study to Evaluate the Effect of Celecoxib on the Efficacy and Safety of Amlodipine on Renal and Vascular Function in Subjects with Existing Hypertension Requiring Antihypertensive Therapy

Summary

EudraCT number	2016-002214-47
Trial protocol	GB
Global end of trial date	21 July 2017

Results information

Result version number	v1 (current)
This version publication date	10 October 2018
First version publication date	10 October 2018

Trial information

Trial identification

Sponsor protocol code	KIT-302-03-02
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02979197
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kitov Pharma Ltd
Sponsor organisation address	One Azrieli Center, Round Tower, Floor 19, 132 Menachem Begin Road , Tel Aviv, Israel, 6701101
Public contact	Chief Medical Officer/US Agent, Kitov Pharma Ltd, 001 2029652215, paul@kitovpharma.com
Scientific contact	Chief Medical Officer/US Agent, Kitov Pharma Ltd, 001 2029652215, paul@kitovpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 July 2017
Global end of trial reached?	Yes
Global end of trial date	21 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the mean reduction in average daytime (9:00 to 21:00) ambulatory systolic blood pressure (SBPday) after oral administration of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together once a day (qd) for 14 days in adult subjects with existing hypertension is no less than half the mean reduction in SBPday after oral administration of amlodipine tablets (10 mg) given alone (i.e., with matched celecoxib placebo) qd for 14 days in the same population.

Protection of trial subjects:

This study was in compliance with the ethical principles derived from the principles of Good Clinical Practice (GCP) [current International Conference of Harmonization (ICH) guidelines], and the Declaration of Helsinki (1964) including all amendments up to and including the October 2013 revision.

All local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

The safety assessments included clinical laboratory tests (hematology, serum chemistry and urinalysis), Electrocardiogram, Physical examination findings, Orthostatic Hypotension measurements and Vital signs. Adverse events were monitored throughout the study.

Background therapy:

None

Evidence for comparator: -

Actual start date of recruitment	03 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 105
Worldwide total number of subjects	105
EEA total number of subjects	105

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	89
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted across 9 sites in the United Kingdom. The first patient first visit was on the 3rd November 2016. The last patient last visit was on the 21st July 2017.

Pre-assignment

Screening details:

Subjects underwent assessments to determine eligibility at the Initial Screening Visit (Day -14 to -10; 255 subjects), Final Screening Visit (Day -1; 159 subjects), and the morning prior to randomization (Study Day 0; 154 subjects). A total of 150 subjects were screen failures and the remaining 105 were randomized.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

Blinding of the subject and Investigational staff to treatment was achieved by using over-encapsulated (OE) formulations and matched placebo capsules. The appearance of the OE amlodipine tablets and matched placebo capsules were identical. Similarly, the appearance of the OE celecoxib capsules and matched placebo capsules were identical. Each patient kit, and the 2 bottles of study drug within the kit, were labeled in a manner to maintain blinding of the subject and Investigational staff.

Arms

Are arms mutually exclusive?	Yes
Arm title	Amlodipine+Celecoxib

Arm description:

Over-encapsulated 10 mg amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Arm type	Experimental
Investigational medicinal product name	OE 10mg amlodipine besylate tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Investigational medicinal product name	OE 200mg celecoxib capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Arm title	Amlodipine+Placebo
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Arm description:

Over-encapsulated 10 mg amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Arm type	Active comparator
Investigational medicinal product name	OE 10mg amlodipine besylate tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Investigational medicinal product name	Matched placebo capsule for OE celecoxib capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Arm title	Placebo+Placebo
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Arm description:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

Arm type	Sham comparator
Investigational medicinal product name	Matched placebo capsule for OE celecoxib capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Investigational medicinal product name	Matched placebo capsule for OE amlodipine tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

Number of subjects in period 1	Amlodipine+Celecoxib	Amlodipine+Placebo	Placebo+Placebo
Started	48	49	8
Completed	44	45	8
Not completed	4	4	0
Subject unable to commit to study dates	-	1	-
Adverse event, non-fatal	4	2	-
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Amlodipine+Celecoxib
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Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Reporting group title	Amlodipine+Placebo
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Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Reporting group title	Placebo+Placebo
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Reporting group description:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

Reporting group values	Amlodipine+Celecoxib	Amlodipine+Placebo	Placebo+Placebo
Number of subjects	48	49	8
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	39	8
From 65-84 years	6	10	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	55.5	56.7	52.5
standard deviation	± 7.13	± 7.43	± 7.84

Gender categorical			
Units: Subjects			
Female	17	18	4
Male	31	31	4
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Black or African American	1	0	0
White	46	47	7
More than one race	1	1	0
Unkown or not reported	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Region of Enrollment			
Units: Subjects			
United Kingdom	48	49	8
Average daytime (9:00 to 21:00) ambulatory systolic blood pressure measured at Day -1			
Units: mmHg			
arithmetic mean	148.0	150.0	151.5
standard deviation	± 7.95	± 8.25	± 10.91

Reporting group values	Total		
Number of subjects	105		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	89		
From 65-84 years	16		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	39		
Male	66		
Race			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	2		
Black or African American	1		
White	100		

More than one race	2		
Unkown or not reported	0		
Native Hawaiian or Other Pacific Islander	0		
Region of Enrollment			
Units: Subjects			
United Kingdom	105		
Average daytime (9:00 to 21:00) ambulatory systolic blood pressure measured at Day -1			
Units: mmHg			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Amlodipine+Celecoxib
Reporting group description:	
Over-encapsulated 10 mg amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks	
Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks	
Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks	
Reporting group title	Amlodipine+Placebo
Reporting group description:	
Over-encapsulated 10 mg amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks	
Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks	
Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks	
Reporting group title	Placebo+Placebo
Reporting group description:	
Matched placebo capsule for over-encapsulated amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks	
Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks	
Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks	

Primary: Mean Reduction in Average Daytime (9:00 to 21:00) Ambulatory Systolic Blood Pressure (SBPday)

End point title	Mean Reduction in Average Daytime (9:00 to 21:00) Ambulatory Systolic Blood Pressure (SBPday) ^[1]
End point description:	
Intent-to-treat (ITT) population = all randomized subjects with a valid Baseline (Day -1 to Day 0) ambulatory blood pressure monitor (ABPM) measurement. For efficacy analyses, the validity of ABPM measurements was based on valid daytime measurements.	
End point type	Primary
End point timeframe:	
Baseline and 14 days	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, the primary endpoint was the difference in the mean reduction in SBPday from baseline to final measurement between the Amlodipine+Celecoxib and Amlodipine+Placebo arms. A comparison with the Placebo+Placebo arm was not part of the primary endpoint and therefore is not included.

End point values	Amlodipine+Celecoxib	Amlodipine+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: mmHg				
arithmetic mean (standard deviation)	-8.0 (± 8.24)	-9.8 (± 8.89)		

Statistical analyses

Statistical analysis title	StatsAnalysis1 Mean Reduction in Average SBPday
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Statistical analysis description:

Last observation carried forward (LOCF) method was used. Primary efficacy analysis was based on the difference between the Amlodipine+Celecoxib and Amlodipine+Placebo (arms 1 and 2, respectively) in the mean reduction in SBPday from baseline (Day -1) to final (Day 13), where a subject completed the 14-day treatment plan, or to Day 6, where a subject was withdrawn from treatment before the Day 13 dose but after the Day 6 dose, or to baseline, where a subject was withdrawn before the Day 6 dose.

Comparison groups	Amlodipine+Celecoxib v Amlodipine+Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
P-value	= 0.024
Method	t-test, 2-sided

Notes:

[2] - A two-sample t-test was used to test the one-sided hypothesis that treatment with Amlodipine+Celecoxib (arm 1) was non-inferior to half of the effect achieved with Amlodipine+Placebo (arm 2). The primary efficacy endpoint was considered met if the lower limits of the 97.5% one-side confidence interval (CI) for the difference in SBPday reduction in arm 1 and 50% of the mean reduction in arm 2 was less than 0.

Secondary: Mean Change in Body Weight

End point title	Mean Change in Body Weight
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End point description:

ITT population as described for primary outcome

End point type	Secondary
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End point timeframe:

Baseline and 14 days

End point values	Amlodipine+Celecoxib	Amlodipine+Placebo	Placebo+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	48	8	
Units: Kg				
arithmetic mean (standard deviation)	0.3 (± 1.02)	-0.3 (± 1.03)	-1.5 (± 3.95)	

Statistical analyses

Statistical analysis title	StatsAnalysis1 Mean Change in Body Weight
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Statistical analysis description:

A serial gatekeeping strategy was used for the secondary efficacy analyses. If, and only if, statistical significance was achieved for the primary efficacy endpoint (SBPday), a secondary hierarchical analysis was to be used to evaluate the secondary efficacy endpoints and was only to proceed from one secondary efficacy endpoint to the next if the alpha was met for the prior analyses. Mean change in body weight was the 1st of the four secondary efficacy endpoints. LOCF technique was used.

Comparison groups	Amlodipine+Celecoxib v Amlodipine+Placebo v Placebo+Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.006 ^[4]
Method	ANOVA

Notes:

[3] - Analysis of variance (ANOVA) was used to compare the mean changes in body weight from baseline to end of treatment among the three treatment arms. The omni-bus test was to conclude if any differences existed, with post-hoc comparisons identifying specific differences between treatment arms. Any statistically significant differences would be sufficient to pass this gate in the study-wide gate keeping strategy.

[4] - While the ANOVA showed a statistically significant difference between the three treatment arms ($p=0.006$), the pairwise comparisons of the treatment arms did not show any clinically meaningful differences.

Secondary: Mean Reduction in Average 24-hour Ambulatory Systolic Blood Pressure (SBP24h)

End point title	Mean Reduction in Average 24-hour Ambulatory Systolic Blood Pressure (SBP24h) ^[5]
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End point description:

ITT population as described for primary outcome

End point type	Secondary
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End point timeframe:

Baseline and 14 days

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, the secondary endpoint related to SBP24hr was the difference in the mean reduction in SBP24hr from baseline to final measurement between the Amlodipine+Celecoxib and Amlodipine+Placebo arms. A comparison with the Placebo+Placebo arm was not part of this secondary endpoint and therefore is not included.

End point values	Amlodipine+Celecoxib	Amlodipine+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: mmHg				
arithmetic mean (standard deviation)	-8.2 (± 7.80)	-8.5 (± 8.47)		

Statistical analyses

Statistical analysis title	StatsAnalysis1 Mean Reduction in Average SBP24h
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Statistical analysis description:

A serial gatekeeping strategy was used for the secondary efficacy analyses. If, and only if, statistical significance was achieved for the primary efficacy endpoint (SBPday), a secondary hierarchical analysis was to be used to evaluate the secondary efficacy endpoints and was only to proceed from one secondary efficacy endpoint to the next if the alpha was met for the prior analyses. Mean reduction in

SBP24h was the 2nd of the four secondary efficacy endpoints. LOCF technique was used.

Comparison groups	Amlodipine+Celecoxib v Amlodipine+Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.826
Method	t-test, 2-sided

Notes:

[6] - A two-sample t-test for superiority was used to test the one-sided hypothesis that treatment with Amlodipine+Celecoxib lowered SBP24h to a greater degree than Amlodipine+Placebo.

Secondary: Mean Reduction in Average 24-hour Ambulatory Diastolic Blood Pressure (DBP24h)

End point title	Mean Reduction in Average 24-hour Ambulatory Diastolic Blood Pressure (DBP24h) ^[7]
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End point description:

ITT population as described for primary outcome

End point type	Secondary
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End point timeframe:

Baseline and 14 days

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, the secondary endpoint related to DBP24hr was the difference in the mean reduction in DBP24hr from baseline to final measurement between the Amlodipine+Celecoxib and Amlodipine+Placebo arms. A comparison with the Placebo+Placebo arm was not part of this secondary endpoint and therefore is not included.

End point values	Amlodipine+Celecoxib	Amlodipine+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: mmHg				
arithmetic mean (standard deviation)	-4.4 (± 4.68)	-3.8 (± 5.27)		

Statistical analyses

Statistical analysis title	StatsAnalysis1 Mean Reduction in Average DBP24h
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Statistical analysis description:

A serial gatekeeping strategy was used for the secondary efficacy analyses. If, and only if, statistical significance was achieved for the primary efficacy endpoint (SBPday), a secondary hierarchical analysis was to be used to evaluate the secondary efficacy endpoints and was only to proceed from one secondary efficacy endpoint to the next if the alpha was met for the prior analyses. Mean reduction in DBP24h was the 3rd of the four secondary efficacy endpoints. LOCF technique was used.

Comparison groups	Amlodipine+Celecoxib v Amlodipine+Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.5
Method	t-test, 2-sided

Notes:

[8] - A two-sample t-test for superiority was used to test the one-sided hypothesis that treatment with Amlodipine+Celecoxib lowered DBP24h to a greater degree than Amlodipine+Placebo. Note, although the alpha was not met for the SBP24h efficacy endpoint of the serial gate-keeping strategy, DBP24h was

Secondary: Mean Change in Creatinine Clearance

End point title	Mean Change in Creatinine Clearance ^[9]
End point description:	
ITT population as described for primary outcome	
End point type	Secondary
End point timeframe:	
Baseline and 14 days	

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Renal function was analyzed by evaluating the decreases in mean serum creatinine from baseline to Day 14 WITHIN EACH TREATMENT ARM, as well as BETWEEN TREATMENT ARMS. The within arm comparisons (i.e., mean decrease from baseline to Day 14) were conducted as three separate analyses, one for each of the three treatment arms. The between treatment arm comparisons (i.e., mean decrease from baseline to Day 14 between arms) were conducted as three separate PAIRWISE comparisons.

End point values	Amlodipine+Celecoxib	Amlodipine+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: mL/min				
arithmetic mean (standard deviation)	4.9 (± 10.62)	3.4 (± 20.96)		

Statistical analyses

Statistical analysis title	StatsAnalysis1 Mean Change in Creatinine Clearance
Statistical analysis description:	
A serial gatekeeping strategy was used for the secondary efficacy analyses. If, and only if, statistical significance was achieved for the primary efficacy endpoint (SBPday), a secondary hierarchical analysis was to be used to evaluate the secondary efficacy endpoints and was only to proceed from one secondary efficacy endpoint to the next if the alpha was met for the prior analyses. Mean change in creatinine clearance was the 4th of the 4 secondary efficacy endpoints. LOCF technique was used.	
Comparison groups	Amlodipine+Celecoxib v Amlodipine+Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.668 ^[11]
Method	t-test, 2-sided

Notes:

[10] - A two-sample t-test for superiority was used to test the one-sided hypothesis that treatment with Amlodipine+Celecoxib improved creatinine clearance to a greater degree than Amlodipine+Placebo. Note, although the alpha was not met for the DBP24h efficacy endpoint of the serial gate-keeping strategy, creatinine clearance was still evaluated for informational purposes and the results are presented here.

[11] - Creatinine clearance increased from baseline to end of study in both arms; however, the superiority of Amlodipine+Celecoxib over Amlodipine+Placebo was not demonstrated. See further evaluation of renal function under serum creatinine outcome.

Secondary: Incidence of Treatment Emergent Adverse Events

End point title	Incidence of Treatment Emergent Adverse Events
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End point description:

Treatment emergent adverse events (TEAEs) included any untoward medical occurrence that initiated or worsened after the first dose of study drugs and within 14 days of the last dose of study drugs.

End point type	Secondary
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End point timeframe:

1 month

End point values	Amlodipine+Celecoxib	Amlodipine+Placebo	Placebo+Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	49	8	
Units: Subjects				
number (not applicable)	35	32	6	

Statistical analyses

Statistical analysis title	StatsAnalysis1 Incidence of Treatment Emergent AEs
Comparison groups	Amlodipine+Celecoxib v Amlodipine+Placebo v Placebo+Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority ^[12]
P-value	= 0.675
Method	Chi-squared

Notes:

[12] - Differences in the incidence of TEAEs between treatment arms were evaluated using Chi-square test.

Statistical analysis title	StatsAnalysis2 Incidence of Treatment Emergent AEs
Comparison groups	Amlodipine+Celecoxib v Amlodipine+Placebo
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.555
Method	Regression, Logistic

Notes:

[13] - Amlodipine+Celecoxib and Amlodipine+Placebo arms were compared by logistic regression, where TEAE (1=at least one TEAE occurred for the subject; 0=otherwise) as dependent variable and treatment as fixed effect.

Secondary: Non-transformed Plasma Concentration of Amlodipine

End point title	Non-transformed Plasma Concentration of Amlodipine ^[14]
End point description:	Pharmacokinetic (PK) population = all subjects enrolled at an Investigational Site with ultraviolet- (UV-) shielded lights who had blood drawn on Day 14, 24 hours ± 1 hour after receiving the final dose of study drugs for the measurement of plasma amlodipine concentration; only treatment arms that included amlodipine were included in the analyses.
End point type	Secondary

End point timeframe:

24 hours post-dose on Day 14

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, no "amlodipine" PK statistical analyses were performed for the PK subjects in the placebo + placebo arms (i.e., the arms that did not receive amlodipine). No subjects in these arms had detectable levels of amlodine in their plasma, and as such, PK analysis was not possible for these subjects.

End point values	Amlodipine+Celecoxib	Amlodipine+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: ng/mL				
arithmetic mean (standard deviation)	15.9 (± 5.72)	18.3 (± 7.21)		

Statistical analyses

Statistical analysis title	Nontransformed PlasmaConcentration of Amlodipine
Statistical analysis description:	
For this analysis, all values below the limit of quantification were treated as 0.	
Comparison groups	Amlodipine+Celecoxib v Amlodipine+Placebo
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.226
Method	t-test, 2-sided

Secondary: Log-transformed Plasma Concentration of Amlodipine

End point title	Log-transformed Plasma Concentration of Amlodipine ^[15]
End point description:	
PK population = all subjects enrolled at an Investigational Site with ultraviolet- (UV-) shielded lights who had blood drawn on Day 14, 24 hours ± 1 hour after receiving the final dose of study drugs for the measurement of plasma amlodipine concentration; only treatment arms that included amlodipine were included in the analyses.	
End point type	Secondary
End point timeframe:	
24 hours post-dose on Day 14	

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, no "amlodipine" PK statistical analyses were performed for the PK subjects in the placebo + placebo arms (i.e., the arms that did not receive amlodipine). No subjects in these arms had detectable levels of amlodine in their plasma, and as such, PK analysis was not possible for these subjects.

End point values	Amlodipine+Celecoxib	Amlodipine+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: ng/mL				
arithmetic mean (standard deviation)	2.7 (± 0.44)	2.8 (± 0.36)		

Statistical analyses

Statistical analysis title	Log-transformed Plasma Concentration of Amlodipine
Statistical analysis description:	
For this analysis, all values below the limit of quantification (BLQ) were treated as 0.04 ng/mL. Assignment of BLQ values to a nonzero number allowed computation of the log transformation. The selection of 0.04 ng/mL was based on the lower limit of quantification of the validated bioanalytical method (0.05 ng/mL) and selecting the next lowest number at the hundredth decimal place.	
Comparison groups	Amlodipine+Celecoxib v Amlodipine+Placebo
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.215
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

1 month; TEAEs include any untoward medical occurrence that initiated or worsened after the first dose of study drugs and within 14 days of the last dose of study drugs.

Adverse event reporting additional description:

Subjects were instructed to report all adverse events (AEs) experienced during the study, and subjects were assessed for the occurrence of AEs throughout the study. Secondary safety assessments included physical examination, body weight, vital signs, orthostatic hypotension evaluations, ECG, hematology, serum chemistry, and urinalysis.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Amlodipine+Celecoxib
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Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Reporting group title	Amlodipine+Placebo
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Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Reporting group title	Placebo+Placebo
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Reporting group description:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

Serious adverse events	Amlodipine+Celecoxib	Amlodipine+Placebo	Placebo+Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 48 (0.00%)	0 / 49 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Amlodipine+Celecoxib	Amlodipine+Placebo	Placebo+Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 48 (52.08%)	23 / 49 (46.94%)	6 / 8 (75.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 48 (4.17%)	2 / 49 (4.08%)	2 / 8 (25.00%)
occurrences (all)	2	2	2
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 48 (10.42%)	9 / 49 (18.37%)	2 / 8 (25.00%)
occurrences (all)	10	10	3
Dizziness			
subjects affected / exposed	3 / 48 (6.25%)	1 / 49 (2.04%)	0 / 8 (0.00%)
occurrences (all)	4	1	0
Lethargy			
subjects affected / exposed	0 / 48 (0.00%)	0 / 49 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	7 / 48 (14.58%)	4 / 49 (8.16%)	0 / 8 (0.00%)
occurrences (all)	7	5	0
Chest discomfort			
subjects affected / exposed	0 / 48 (0.00%)	0 / 49 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	2 / 48 (4.17%)	0 / 49 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Feeling cold			
subjects affected / exposed	0 / 48 (0.00%)	0 / 49 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

Feeling hot subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	3 / 49 (6.12%) 6	0 / 8 (0.00%) 0
Pain subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 49 (0.00%) 0	1 / 8 (12.50%) 2
Eye disorders Eye swelling subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 49 (0.00%) 0	1 / 8 (12.50%) 1
Vision blurred subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 49 (0.00%) 0	1 / 8 (12.50%) 1
Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 49 (2.04%) 1	1 / 8 (12.50%) 1
Flatulence subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 49 (0.00%) 0	1 / 8 (12.50%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	2 / 49 (4.08%) 2	1 / 8 (12.50%) 1
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	2 / 49 (4.08%) 2	1 / 8 (12.50%) 1
Rash subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	0 / 49 (0.00%) 0	0 / 8 (0.00%) 0
Musculoskeletal and connective tissue disorders Joint swelling subjects affected / exposed occurrences (all)	10 / 48 (20.83%) 12	9 / 49 (18.37%) 13	1 / 8 (12.50%) 1
Arthralgia			

subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	3 / 49 (6.12%) 8	0 / 8 (0.00%) 0
Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Sinusitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 49 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No limitations

Notes: